

## Jugulotympanic paragangliomas: 75 years of evolution in understanding

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Jugulotympanic paragangliomas were first described approximately 75 years ago. Since that time, there has been considerable evolution in knowledge of tumor biology, methods of classification, and appropriate management strategies. This paper attempts to summarize these gains in information. (<http://thejns.org/doi/abs/10.3171/2012.6.FOCUS12138>)

**KEY WORDS** • **glomus jugulare tumor** • **paraganglioma** • **tumor biology**

**P**ARAGANGLIOMAS, also known as chemodectomas or glomus tumors, arise from rests of paraganglionic tissue. These rests of tissue, sometimes referred to as “paraganglions,” are often found immediately adjacent to sympathetic ganglia along the aorta and its branches. While it was originally believed that paragangliomas originated from true glomus complexes, this theory has been proven false and the commonly used term “glomus tumor” is actually a misnomer.<sup>14</sup> There are 4 common sites of extraadrenal paragangliomas: the inferior ganglion or ganglion nodosum of the vagus nerve (glomus vagale tumors), the carotid artery bifurcation (carotid body tumors), the jugular fossa (glomus jugulare tumors), and the middle ear (glomus tympanicum tumors). The purpose of this paper is to describe the evolution in understanding of the latter 2 types of tumors, so-called jugulotympanic paragangliomas.

### Early History

In 1941, Rufus Guild<sup>17</sup> first used the term glomus jugulare, or jugular body, to define paraganglionic tissue found in close proximity to the jugular bulb. Using temporal bone sectioning, Guild demonstrated that jugular body tissue was almost always found in 1 of 3 locations: approximately half of the time, jugular bodies were lo-

cated in the adventitia of the dome of the jugular bulb;<sup>16</sup> in the remaining specimens, the jugular bodies occurred with apparent equal frequency in either the tympanic branch of the glossopharyngeal nerve, or the auricular branch of the vagus nerve. In 1945, Harry Rosenwasser<sup>47</sup> expanded on Guild’s work by proposing that the aforementioned tissue was a precursor to vascular, “glomus” tumors of the middle ear. While this was the first known description of glomus tumors in the English literature, it is notable that J. Lubbers had provided a similar description in the Dutch literature 8 years prior.<sup>54</sup> It was later demonstrated that these glomus tumors could occur in either the region of the jugular bulb or in the middle ear, findings in strong correlation with the anatomical descriptions provided by Guild.

Over the next 2 decades, Rosenwasser<sup>48–53</sup> recorded a series of 36 glomus tumors and described his experiences at the time as part of a series of monographs detailing the initial discoveries by multiple surgeons, the pathology of the disease process, its diagnosis, and its treatment options. This was the largest series of glomus tumors ever reported at that time.

### Evolution in Tumor Classification

In the years following the initial description by Rosenwasser, jugulotympanic paragangliomas were often colloquially assigned to 1 of 2 designations: those that involved the middle ear were referred to as glomus tym-

Abbreviation used in this paper: SDHD = succinyl dehydrogenase.

panicum tumors, and those that involved the infralabyrinthine region were referred to as glomus jugulare tumors.<sup>3</sup> While this system was both simple and reliable, the above terms failed to accurately describe many important tumor characteristics integral to surgical decision making. Because imaging at the time was still very preliminary, largely consisting of subtle findings on plain radiographs, patient symptomatology and findings on physical examination contributed heavily to surgical planning. Alford and Guilford<sup>3</sup> attempted to reclassify the natural history of the tumors based on patient symptoms, ear findings on physical examination, radiographs, and cranial nerve examination. For the most part, limitations in classification during this era impeded communication, and therapeutic strategies varied widely.

In 1979, Oldring and Fisch<sup>42</sup> described a classification system they had constructed following a retrospective review of 23 patients with glomus tumors who underwent surgical treatment. This system was the first true attempt to stratify glomus tumors based on anticipated surgical approach; the system placed tumors into different groups using criteria of size and anatomical extent. In the Fisch system, tumors limited to the tympanic region and middle ear cleft were designated as Type A tumors, also known as glomus tympanicum tumors. These tumors were resected via a transmeatal tympanotomy. Tumors involving the middle ear with extension to the mastoid portion of the temporal bone, but without destruction of infralabyrinthine temporal bone, were designated as Type B tumors. As a general rule, these were resected via a combined transmeatal and transmastoid approach. Tumors with infralabyrinthine extension and/or extension toward the petrous apex with destruction of infralabyrinthine temporal bone were designated Type C tumors, and required a combination of an infratemporal dissection and mastoidectomy with mobilization of the facial nerve and ligation of the sigmoid sinus. Tumors with intracranial extension were designated Type D tumors. Type D tumors were further subclassified as D1, in which the intracranial extension was less than 2 cm in diameter, and D2, for tumors in which the intracranial extension exceeded 2 cm. The authors recommended a 2-stage operation for Type D tumors: removal of the intracranial portion of the tumors by neurosurgery, followed by neurotological removal of the intratemporal portion 4–6 weeks later. However, an exception was made in Type D tumors in which resection was believed to be impossible; in these cases radiotherapy was recommended.<sup>42</sup>

In response to further advances in neurotologic surgery, Jackson et al.<sup>25</sup> proposed a revision to the Fisch classification in 1982. The Glasscock-Jackson classification system departed from the Fisch system by attributing a great deal of importance to tumor origin (utilizing concepts described by Alford and Guilford 20 years prior), and further subdividing the anatomical boundaries from the Fisch classification using a more intricate assessment of the extent of tumor invasion.<sup>13</sup> Unlike other proposed classification schemes, the classification systems constructed by Dr. Fisch and Dr. Glasscock provided considerable guidance to surgical planning and therefore remain the two most commonly used systems today.

## Evolution in Tumor Management

The difficult location, complex anatomy, and dense vascularity of these tumors complicated initial attempts at resection.<sup>62</sup> Results published in the formative years of treatment were less than optimal; patients often received subtotal resection in combination with radiotherapy, or simply radiation alone.<sup>7</sup> Over time, however, stepwise improvements in both the surgical and nonsurgical armamentaria allowed for the evolution of safe and appropriate management strategies. What follows is a brief summary of this evolution in management; for a more comprehensive review of the history of surgical management of glomus tumors, the authors recommend the excellent report by Michael and Robertson.<sup>37</sup>

One of the earliest known descriptions of attempted resection of jugulotympanic paragangliomas was provided by Rosenwasser following a procedure in April 1942.<sup>47</sup> In this article, he described the resection of a “bleeding mass which arose in the middle ear” and compared the neoplasm to Guild’s previous description of a glomus tumor. Further advancements came in 1949, when Lundgren<sup>33</sup> described the first exploration of the jugular bulb. This report represented an important step in unlocking the delicate anatomy of the jugular foramen and bulb region. Subsequent to this paper, Rosenwasser’s case series of 36 patients<sup>48–53</sup> added considerably to the growing body of knowledge. This series included a description of catecholamine secretion during tumor removal that resulted in cardiac instability and death in 1 patient; the repercussions of this report resulted in a significant alteration in how surgeons and anesthesiologists approached preoperative blood work. Rosenwasser also described the first case of distant metastasis in jugulotympanic paragangliomas, demonstrating the potential for malignancy even after successful local resection. Perhaps of greatest importance, Rosenwasser<sup>51</sup> became one of the first to offer a surgical algorithm for management of these tumors. Small tumors with confinement to the middle ear were recommended for removal via a transtympanic approach, as described by Julius Lempert. In tumors with extension to the mastoid, a mastoidectomy for gross-total resection was recommended. Management of the remaining group of tumors (those found to have extension through the temporal bone and/or intracranial extension) was influenced by reports by Shambaugh,<sup>13</sup> Shapiro and Neues,<sup>55</sup> Guilford and Alford,<sup>3</sup> and Weille.<sup>60</sup> In this final group, wide resection with control of the vessels in the neck, and postoperative radiation for incomplete tumor removal, was advocated.

At approximately the same time Rosenwasser was publishing his clinical experience with jugulotympanic paragangliomas, other authors were reporting on various advances in surgical management. Weille and Lane<sup>60</sup> published a detailed report of Weille’s operative technique in a patient found to have an extensive jugulotympanic paraganglioma. This report proposed advancements in visualization as a result of more aggressive removal of adjacent temporal bone. It is clear in the paper that fear of uncontrollable hemorrhage prevented the authors from attempting removal of the jugular bulb, a common limita-

## History of jugulotympanic paragangliomas

tion of the era (2 radon seeds were placed in the surgical bed postoperatively to help with control of the subtotally resected neoplasm). As surgeons became more familiar with the neoplastic process, attempts at resection began to increase in frequency in the 1950s. One year following the report by Weille and Lane, Capps<sup>7</sup> reported subtotal resection of a glomus jugulare tumor. This operative description was notable because an (unsuccessful) attempt was made to resect the jugular bulb; equally notable, this report provided the first description of facial nerve mobilization.

Advances in external beam radiation therapy for jugulotympanic paragangliomas occurred contemporaneously with surgical gains of the 1950s.<sup>6,31</sup> The Mayo Clinic protocol, published in 1955,<sup>61</sup> consisted of delivery of 13–20 Gy to the tumor bed over an approximate 2-week period. External beam radiation therapies varied with location and evolved with time.<sup>23</sup> The protocol in place at M.D. Anderson Cancer Center from 1944 to 1964 consisted of administering 45 Gy to the tumor bed over 35 days.<sup>32</sup> It is important to note that the majority of patients included in these initial reports received radiation therapy following subtotal resection, and that radiation was not considered primary therapy outside of palliation for neoplasms believed to be inoperable. Despite its restricted use, these preliminary forms of radiotherapy were believed to be relatively effective; a meta-analysis of treatments performed prior to 1981 reported acceptable local control in 91% of patients, with low rates of morbidity.<sup>57</sup>

Continuing into the 1960s, a series of radiographic advances led to improved planning and further advances in surgical technique. Improvements in angiography and polytomography allowed surgeons to gain a more accurate preoperative perception of tumor localization.<sup>37</sup> One of the initial reports of jugular bulb removal and gross-total tumor resection was described by Shapiro and Neues in 1964.<sup>55</sup> This report was one of the first to advocate wide exposure of neck anatomy; the access to the external carotid artery and internal jugular vein that accompanied this exposure allowed better control of hemorrhage. Prior to this report, the fear of uncontrollable bleeding hindered attempts at gross-total resection. Further advances in technique were reported in 1965, when Gejrot<sup>2,10</sup> described preservation of the medial wall of the sigmoid sinus, a surgical tenet designed to protect the lower cranial nerves that remains widely advocated today. Gejrot also described complete isolation of the venous system by packing off the mastoid and ligating the jugular vein to safely resect the bulb with minimal bleeding. Additional variations in surgical approach were described in ensuing years; among these variations, House et al.<sup>35,43</sup> reported their preference for use of the facial recess corridor in 1969, describing new techniques useful for resection of tumors confined to the jugular foramen without significant internal carotid artery involvement. Use of the facial recess permitted surgeons to remove tumor from the middle ear and hypotympanum as well as the mastoid, without removing the canal wall. Prior to this advancement, radical mastoidectomies were often needed for sufficient removal of tumor. This procedure left patients with large ear defects and poor hearing, and committed them to a

lifetime of aural care. With the facial recess approach, both hearing and the external auditory canal could potentially be preserved.

Further advances were reported in 1977, when Fisch<sup>9</sup> described operative maneuvers to gain control of the petrous carotid artery, a technique useful in tumors extending to involve the carotid artery. Despite the magnitude of these reports, the most significant advancement of the 1970s came with the introduction of preoperative embolization of jugulotympanic paragangliomas. This adjunctive therapy was introduced in 1975<sup>22</sup> and later validated in a publication by Simpson et al. in 1979.<sup>56</sup> Results in these formative years of endovascular treatment were limited by available technology, in which decreased pliability and control of microcatheters in this era required direct carotid puncture to allow for adequate maneuverability.<sup>22</sup> Furthermore, bulkier embolization materials (including silastic spheres and Gelfoam) and larger microcatheters prevented superselective embolization beyond tertiary branches of the external carotid artery. As a result, morbidity in early series was much higher than it is today; the series by Hlal and Michelsen<sup>22</sup> reported a mortality rate of 12.5% in patients with glomus jugulare tumors who underwent embolization. Evolution in technology has allowed for significant decreases in the incidence of complications and death in modern series, and deaths from this modality have become increasingly rare. Multiple subsequent publications have confirmed reductions in both operative duration and intraoperative blood loss,<sup>30,39</sup> and preoperative embolization remains an imperative part of contemporary management of jugulotympanic paragangliomas.

The application of radiation therapy again witnessed significant advances at the end of the twentieth century. The limitations of external beam radiotherapy, including the need for multiple sessions, large radiation fields, and relatively imprecise targeting, were obviated when Gamma Knife surgery was introduced for these neoplasms in the early 1990s.<sup>19,29</sup> The increased conformity, hypofractionation (requirement of < 5 treatment sessions), and steep radiation falloff of radiosurgery was attractive to practitioners. With time, the use of stereotactic radiosurgery as a primary therapy for a subset of neoplasms has gained acceptance. While long-term data (> 10 years) in patients with jugulotympanic neoplasms who undergo radiation therapy is somewhat limited, data that do exist suggest reasonable progression-free survival, reported as 75% at 10 years by Pollock.<sup>44</sup>

In 1987, Al-Mefty et al.<sup>1</sup> described a combined approach for giant glomus tumors with intracranial extension, previously believed to be inoperable, again expanding the spectrum of tumors amenable to resection. The ability to achieve effective gross-total resection in the microsurgical era was illustrated in 2001<sup>26</sup> in one of the largest series of glomus tumors to date. In this publication, Jackson et al.<sup>26</sup> reported on the surgical results following 182 procedures for resection of glomus tumors involving the skull base; 152 of the procedures involved jugulotympanic glomus tumors. Complete surgical control, defined as a patient remaining alive without any evidence of tumor burden throughout the entire follow-up period, was achieved in 85% of cases, and there were 9 cases (5.5%)

of recurrence. New deficits in cranial nerves IX, X, XI, and XII occurred in 39%, 25%, 26%, and 21% of cases, respectively. This report is of historical significance as opinions on the relative importance of gross-total resection and new cranial nerve deficit have changed since the time of publication. In recent years, many skull base surgeons have come to embrace a philosophy in which some degree of subtotal resection is accepted in exchange for maintenance of cranial nerve function whenever possible.

Given the various management options available to the surgeon for management of these neoplasms, Ivan et al.<sup>24</sup> undertook a meta-analysis to assess tumor control rates and treatment-related morbidity for different management strategies in 2010. Eight hundred sixty-nine patients were stratified based on treatment into subtotal resection alone, gross-total resection alone, subtotal resection combined with stereotactic radiosurgery, or stereotactic radiosurgery alone. Patients undergoing stereotactic radiosurgery alone experienced the lowest rates of recurrence of these 4 cohorts. Additionally, the incidence of cranial nerve IX–XI deficit was found to be higher in gross-total resection than in those who underwent stereotactic radiosurgery alone. These results suggest that radiosurgery should be considered a viable option in the primary treatment of these neoplasms. As long-term data (> 10 years) following stereotactic radiosurgery of these neoplasms is relatively sparse, further analysis appears to be warranted.

### Evolution in Understanding of Tumor Biology

The nomenclature of jugulotympanic paragangliomas has varied over the years, often in response to new revelations in tumor biology. Winship et al.<sup>62</sup> first denoted the neoplasm a “glomus jugularis tumor” in 1948 because the neoplastic cells were believed at the time to have arisen from a glomus body. A year later, these tumors were described as “non-chromaffin paragangliomas” because they histologically resembled paraganglionic tissue but did not stain for chromaffin.<sup>49</sup> Soon thereafter, Mulligan<sup>38</sup> suggested the tumors be referred to as chemodectomas, as they were assumed to arise from chemoreceptor cells. However, in 1953, Gaffney correctly pointed out that these tumors, while histologically similar to paraganglia and not staining for chromaffin, were not, in fact, glomus in character. Nonetheless, this terminology has persisted.

Normal paraganglionic tissue is known to arise from neural crest cells that have migrated and matured into chief cells, which, in turn, are supported by sustentacular cells and small blood vessels in clusters with characteristic cellular architecture known as Zellballen.<sup>17,20</sup> As chief cells are components of the diffuse neuroendocrine system, they are capable of storage and secretion of catecholamines in response to various signals.<sup>58</sup> Approximately 1–3% of jugulotympanic glomus tumors secrete catecholamines in quantities sufficient to cause clinical symptomatology.<sup>20</sup> As with many other components of the diffuse neuroendocrine system, these tumors are associated with a high concentration of somatostatin receptor sites on the cellular surface.<sup>46</sup> Clinically, this permits imaging with somatostatin receptor scintigraphy and radiolabeled octreotide. This form of imaging can be used to supplement

more traditional modalities, such as MRI or CT, and can be especially useful in detecting metastases in the approximately 5% of these tumors associated with malignancy.<sup>18</sup> In addition to radiographic localization, scattered case reports have suggested that therapy with octreotide might provide an additional form of control in inoperable or recurrent tumors that are unresponsive to radiation therapy.<sup>28,45</sup>

Although the majority of glomus tumors are now known to arise from sporadic mutations, familial inheritance with known genetic defects constitutes 10–20% of these neoplasms.<sup>20,36</sup> Familial sympathetic paragangliomas can present in the setting of a known syndrome such as Von Hippel-Lindau syndrome, neurofibromatosis Type I, and multiple endocrine neoplasia Types IIA and IIB; alternatively, this disorder can be inherited as an isolated entity secondary to mutation of genes encoding the subunits of the mitochondrial enzyme SDHD,<sup>15</sup> a protein involved in the Krebs cycle and mitochondrial electron-transport chain. Baysal<sup>5</sup> has proposed that mutations in SDHD lead to a perceived hypoxic state and subsequent hypoxia-induced cellular hyperplasia and, potentially, neoplasia. The first loci responsible for familial glomus tumors, *PGL1* and *PGL2*, were identified on chromosome 11 in 1992 and 1995, respectively.<sup>21,34</sup> The next loci, *PGL3* and *PGL4*, were identified 7 years later on chromosome 1.<sup>4,40,41</sup> Because 3 of the mutated gene products of the PGL loci are subunits of SDHD, these mutations have now been renamed as *SDHD* (*PGL1*), *SDHC* (*PGL3*), and *SDHB* (*PGL4*) to more accurately reflect the protein subunit with the mutation.<sup>8</sup> However, to date, the origin of Type 2 familial paraganglioma syndrome (*PGL2*) remains unknown. Inheritance of these mutations occurs in an autosomal dominant fashion with age-dependent and incomplete penetrance.<sup>5</sup> In SDHD mutations, the erratic sequence is transmitted from affected fathers, suggestive of maternal imprinting.

While the aforementioned discoveries have shed light on familial paragangliomas, the pathophysiology of the approximately 80% of nonfamilial glomus tumors remains less certain. Given the dense vascularity of these lesions, faulty angiogenesis has been implicated and many authors have suggested that the small-molecule vascular endothelial growth factor may play a role in tumorigenesis.<sup>27,59</sup> This hypothesis is supported by human studies in which mutations in *SDHB* and *SDHD* genes cause mitochondrial dysfunction as well as upregulation of vascular endothelial growth factor and receptors.<sup>11,12</sup> However, whether these findings will lead to a potential intervention remains uncertain.

The past decade has brought about significant advances in understanding the biology of these tumors. The mitochondrial chain, pathological angiogenesis, and somatostatin signaling represent 3 potential pathways in which further advances in small-molecule therapy might potentially lead to medical treatments for this intriguing neoplasm.

### Conclusions

Although jugulotympanic paragangliomas have been

## History of jugulotympanic paragangliomas

documented in the medical literature for well over half a century, knowledge about appropriate management strategies and tumor biology continues to evolve. This paper summarized many of the gains in understanding of these tumors that have occurred over the past 75 years. It is our hope that a better understanding of the past will help provide patients with better surgical planning and treatment options in the future.

### Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Forbes, Thompson, Haynes, Tsai. Drafting the article: Forbes, Brock, Tsai. Critically revising the article: Forbes, Ghiassi, Thompson. Reviewed submitted version of manuscript: Forbes. Approved the final version of the manuscript on behalf of all authors: Forbes.

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